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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,525	01/10/2001	Peng George Wang	10114/6	9752

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,525	WANG ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-48 and 52-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-48 and 52-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1.10.2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants amendment and response filed June 27, 2005, is acknowledged. Claims 39-48 & 52-70, are under consideration in this examination.

2. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

3. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

4. Claims 49 & 71-76 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed.

5. ***Sequence Rules***

The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a) and (a)(2). However, the specification fails to comply with one or more of the requirements of 37 CFR § 1.821 through 1.825 as follows: Applicants' submission of a hard copy "Sequence Listing" as required by 37 CFR § 1.821(d) as well as in computer readable form (CRF), filed November 4, 2004, is acknowledged. Appropriate corrections for compliance is required, which includes resubmission of the CRF and a hard copy of the sequence listing, along with a statement that the information contained in the hard copy and the CRF are identical.

CRF problem report enclosed previously, to aid the Applicants in the correction for sequence compliance.

CRF problem is related to Applicants' 'sequence listing' filed 10.22.2002, NOT November 4, 2004 as argued by the Applicants. Compliance is required.

6. ***Claim Rejections - 35 USC § 112*** (first paragraph)

Claims 39-48 & 52-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell transformed with a nucleic acid encoding a sugar-nucleotide regenerating enzyme viz., (1) galactokinase (GalK), (2) galactose-1-phosphate uridylyltransferase (GalT), (3) glucose-1-phosphate uridylyltransferase (GalU) and (4) pyruvate kinase (PykF); and a glycosyltransferase, viz., (5) I1, 3-galactosyltransferase, all from *E.coli*, for the production of oligosaccharides (α-galactose), does not reasonably provide enablement for the transformation of host cell(s) using any or all the five 5 enzymes (as described above in 1-5) of the biosynthetic pathway for the formation of α-galactose from any source. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 39-48 & 52-70 are so broad as to encompass a cell comprising one or more sugar nucleotide regenerating enzyme and one or more glycosyltransferase from any source for the production of any glycoconjugate, which may includes an oligosaccharide, a glycoprotein, a glycolipid, among others. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sugar nucleotide regenerating enzyme(s) and glycosyltransferase(s), from any source, broadly encompassed by the claims.

The specification provides the construction of single super bug or cell comprising (1) galactokinase (GalK), (2) galactose-1-phosphate uridylyltransferase (GalT), (3) glucose-1-phosphate uridylyltransferase (GalU) and (4) pyruvate kinase (PykF); and a glycosyltransferase, viz., (5) I1, 3-galactosyltransferase, all from *E.coli*, for the production of oligosaccharides (α-galactose).

The prior art describes the glycosyltransferases to be a large family of enzymes that participates in a concerted fashion in the biosynthesis of polysaccharides, and of carbohydrate moieties of glycoproteins and glycolipids.

The sequence-function relationship of this class of proteins in prokaryotes and Eukaryotes class of proteins has been recently reviewed [see Breton et al. J. Biochem. 123, 1000-1009 (1998), see abstract, **IDS**], The results of this study allowed the grouping of 12 groups of glycosyltransferases into 5 families. Using a conserved graphics method for protein comparison, conserved structural features were found in some of the glycosyltransferase groups, indicating lack of conserved sequences among the glycosyltransferase(s) family. Further distinction has been observed among the glycosyltransferases from Prokaryotes and Eukaryotes. In eukaryotes, glycosyltransferases consist of a short N-terminal cytoplasmic tail, a transmembrane domain, a stem region of variable length and a large C-terminal globular catalytic domain. This is in contrast to bacterial (prokaryotic) glycosyltransferases, some having several transmembrane domains, whereas others bind to membranes even though no membrane domains were predicted [see, Breton et al. (1998), page 1000, column 1-2]. The glycosyltransferases constitute a large heterogeneous class of enzymes, some families include enzymes that catalyze different reactions (see, Breton et al. concluding remarks on page 1007). Since the amino acid sequence of an enzyme determines its structural and functional properties, and because there appears to be a large variation among the different types of glycosyltransferases as well as the source from it is obtained, inserting these genes from any source into a cell construct will not only be undue but lead to transformed cell incapable of yielding the desired product in view of the different members of the enzyme catalyzing different reactions.

While recombinant techniques are known, it is not routine in the art to screen for multiple genes from a variety of sources, to obtain sugar nucleotide regenerating enzyme viz., Ga1k or GalT or GaIU or Pykf or Ndk or PpK or AcK or PoxB or Ppa or PgM or NagE or Agml or glmu or GalNAc kinase or pyrophosphorylase or Ugd or NanA or Cmk or NeuA or A1g2 or Algl or SusA or ManB or ManC or phosphomannomutase or Ga1E or GMP or GMD or GFS

from any source; **and/or** a glycosyltransferase enzyme from among - LgtB, LgtC (galactosyltransferase); Lgtf, Alg5 or DUGT (glucosyltransferase); LgtA (N-acetylglucosaminyl transférase); UDP-GalNAc:2'-fucosylgalactiside-I-3-N-acetylgalactosaminyl transferase; UGT2B7 (glucoronyltransferase); SiaT0160 (sialyltransfearse); Alg1 or Alg2 (mannosyltransferase); I 1,3-FucT or I 1,2-FucT or I 1,3,4-FucT (fucosyltransferases)] from any source and integrate into the genome of the cell, as encompassed by the instant claims, and/or transform any cell with these genes in various combination(s) irrespective of the biosynthetic pathway or sequential steps, to obtain the desired product would be highly unpredictable and with no reasonable expectation of success in obtaining the desired construct/ activity/product, because of insufficient guidance.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any cell comprising one or more sugar-nucleotide regenerating enzyme and one or more glycosyltransferase from any source. Such a cell, which is not isolated, may be human cell and which may read on a human being and such a scope is not enabled. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of cell construct comprising equivalent sequence as relevant to the metabolic or biosynthetic pathway in question, and having the capability of producing the desired biological product(s) is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments:

Referring to various pages in the instant specification, Applicants argue that the specification can be used as a guide for one skilled in the art to make and use a cell that produces glycoconjugates.

One of skill in the art can certainly use the instant specification as a guide to make and use a cell that produces glycoconjugates, but the question is to what extent. As explained in the enablement rejection guidance is limited to the construction of single super bug or isolated ***E. coli*** cell comprising (1) galactokinase (GalK), (2) galactose-1-phosphate uridylyltransferase (GalT), (3) glucose-1-phosphate uridylyltransferase (GalU) and (4) pyruvate kinase (PykF); and a glycosyltransferase, viz., (5) I1, 3-galactosyltransferase, all from *E.coli*, for the production of α-galactose, an oligosaccharide.

Applicants submit in Appendix A post-filing publications describing the creation of specific constructs and their expression in E. coli, predominantly. Applicants' claims are, however, not drawn to a small number of specific construct or the specific E. coli. host cell comprising the specific genes, are therefore not enabling.

There is no guidance to transforming any type of cell (claims 39, 46-48 & 52-70) with an entire laundry list of genes (see claim 52, for example) from any source, some/many not yet characterized. Further, reasons are as explained in the rejection, not responded to by the Applicants. The rejection is therefore maintained.

7. Claims 39-48 & 52-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39-48 & 52-70, recite a cell comprising one or more sugar nucleotide regenerating enzyme and one or more glycosyltransferase from any source for the production of any glycoconjugate, which may includes an

oligosaccharide, a glycoprotein, a glycolipid, among others. More specific recitation includes a cell comprising sugar nucleotide regenerating enzyme comprising, Ga1k or GalT or GalU or Pykf or Ndk or PpK or AcK or PoxB or Ppa or PgM or NagE or Agml or glmu or GalNAc kinase or pyrophosphorylase or Ugd or NanA or Cmk or NeuA or A1g2 or Algl or SusA or ManB or ManC or phosphomannomutase or Ga1E or GMP or GMD or GFS from any source; **and/or** a glycosyltransferase enzyme comprising – LgtB, LgtC (galactosyltransferase); Lgtf, Alg5 or DUGT (glucosyltransferase); LgtA (N-acetylglucosaminyl transferase); UDP-GalNAc:2'-fucosylgalactiside-I-3-N-acetylgalactosaminyl transferase; UGT2B7 (glucoronyltransferase); SiaT0160 (sialyltransfearse); Alg1 or Alg2 (mannosyltransferase); I 1,3-FucT or I 1,2-FucT or I 1,3,4-FucT (fucosyltransferases)] from any source.

The specification, however, only provides a single representative species - in the construction of single super bug or cell comprising (1) galactokinase (GalK), (2) galactose-1-phosphate uridylyltransferase (GalT), (3) glucose-1-phosphate uridylyltransferase (GalU) and (4) pyruvate kinase (PykF); and a glycosyltransferase, viz., (5) I1, 3-galactosyltransferase, all from *E.coli*, for the production of oligosaccharides (α-galactose). There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species. The specification also fails to describe additional representative species of these superbugs by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species of these superbugs, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Therefore, the written description requirement is not satisfied.

Applicants' arguments:

Applicants argue that the specification is replete with examples having given activities that may be used together to regenerate sugar nucleotides, and figures providing diagrams of plasmids that are useful in creating the cells of the present claims. The sequences of thousands of sugar nucleotides regenerating enzymes, epimerases, and glycosyltransferases were known in the art at the time of filing. Moreover, the specification provides several working examples of cells of the present invention that produces a glycoconjugate of interest in the absence of an exogenously supplied nucleotide triphosphate and comprises heterologous genes encoding one or more sugar nucleotide regenerating enzyme and one or more glycosyltransferase.

Clearly in the sequence data bases numerous sequences are known. However, the question is how representative are these sequences and the specific *E. coli* constructs comprising the specific enzymes from specific sources to genus being claimed? It is impossible to extrapolate the small set of species description to include a broad genus claimed. There is no description in the specification supportive of transforming any type of cell (claims 39, 46-48 & 52-70) with an entire laundry list of genes (see claim 52, for example) from any source, some/many not yet characterized. The rejection is therefore maintained.

8. 35 U.S.C. 102 (new)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39-42, 50-53 & 62-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Koizumi et al. [Koizumi et al. (1998) Nature Biotechnology, 16:

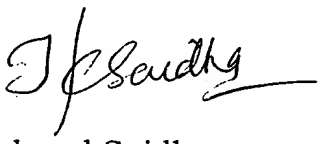
847-850]. Koizumi et al. teach that the production of globotriose (oligosaccharides) was accomplished by coupling a combination of cell constructs – *E. coli* cells transformed with sugar nucleotide regenerating enzyme *galT, GalK,* and *GalU,* and with a glycosyltransferase such as, alpha 1,4-galactosyltransferase gene (lgtC); and where in the cells produces a glycoconjugate, such as globotriose, in the absence of exogenously supplied nucleotide triphosphate. The claims are written so broadly as to be anticipated by the reference.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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